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PATENT SPECIFICATION

NO DRAWINGS

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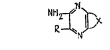
COMPLETE SPECIFICATION

Novel Process for Preparing Heterocyclic Compounds

We, SMITH KLINE & FRENCH LABORATORIES of 1500 Spring Garden Street, City of Philadelphia, Zone 1, Commonwealth of Pennsylvania, United States of America, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a novel process for preparing heterocyclic compounds possessing as an essential part of their nucleus a condensed aromatic pyrazine structure.

The heterocyclic compounds which may be produced by the process of this invention have the following basic structure:



I

in which X together with the two carbon atoms to which it is attached represents an optionally substituted phenyl, naphthyl, pyrimido, pyrazolo or pyrido ring; and R represents an unsubstituted or substituted alkyl group having a maximum of 12 carbon atoms, for example lower alkyl, ω-tertiaryamino-lower alkyl, or cycloalkyl such as cyclohexyl or cyclopentyl; an unsubstituted or substituted aryl group having a maximum of 12 carbon atoms, for example phenyl or thienyl; an alkoxy group having a maximum of 8 carbon atoms, a phenoxy group, or a carbamyl group. The chemical character of R must be such that it is stable toward elimination during the cyclization step of the reaction hereinafter described. For example, it has been found that when R in formula II is an arylmercapto or alkylmercapto residue it is eliminated during cyclization to give the 3-acyl heterocyclic compound rather than the 3-mercapto derivative.

As will be noted hereafter, the basic rings which X represents may be substituted by unreactive radicals common to the art such as by hydroxyl, amino, lower alkylamino, lower dialkylamino, lower alkylthio, lower alkoxy, heterocyclic amino alkyl, phenyl, and thienyl groups. Such substitution will be made as desired by one skilled in the art using known synthetic methods to obtain compounds having desired utility as known to the art. These substituents do not affect the novel reaction of this invention except as described hereafter.

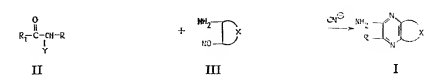
The process of this invention has made possible production of heterocyclic compounds as discussed above in good yield and using nitrosoamines with easily prepared acylmethylene compounds. The process is believed to be novel in that no similar reaction is known to the art.

The compounds produced by the process of this invention have various utilities. Most universal is their use in known reactions as intermediates for preparing medicinally active compounds. Many of the compounds have utility as nuclei for preparing dyestuffs or for their own inherent fluorescence or dyestuff character. Other products have activity in themselves as medicinal agents such as diuretics, antihypertensives, vesodilators for instance coronary arterial dilators, antibacrerials, antifolic acid compounds or microorganism antagonists such as *anti-Lactobacillus casei*, *Streptococcus faecalis*, *Staphylococcus aureus* or *Escherichia coli* agents.

While the nature of the products produced by the process of this invention is not particularly dependent on the nature of the X ring or its substituents the full scope of this invention will be illustrated by concentrating illustrative examples in the pteridine series whose end products are known to have antifolic acid or diuretic/antihypertensive activities. Similar reactions in various series con-

taining other nuclei will be apparent from the examples provided.

The process of this invention comprises reacting an *o*-nitrosoamine (III) with an acylmethylene compound (II) in the presence of cyanide ions to give the desired 2-aminopyrazino heterocyclic end product (I).



II III I

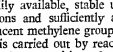
It will be apparent that during the cyclization reaction the acyl group (R_1CO) is eliminated and the cyano group is incorporated into the 2-aminopyrazino ring. Several types of acylmethylene compound have been found to undergo this reaction depending largely on the reactivity of the methylene group and the stability of the R group during cyclization.

When Y is cyano, R may be an aryl or alkyl group, carbamyl, lower alkoxy or phenoxy as defined above. In such case any basic condensing group may be present such as an alkali metal alkoxide, lower alkyl carboxylate, or preferably cyanide. Sodium or potassium cyanide or acetate are preferred.

When Y is hydrogen, the methylene group is much less active and R must be a stable activating group such as an aryl group, for example, phenyl or thienyl, or a carbamyl group. An ourside source of cyanide ions must be present, for example, HCN or an alkali metal cyanide.

When X is a pyridinium or substituted pyridinium group such as $PY^{\oplus}\ Z^{\ominus}$, R may be any group as defined above and an outside source of cyanide ions must also be present. Z may be any suitable anion as known to the art. This acylmethylene compound gives very fast action and in very good yield.

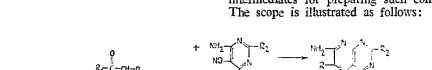
In each of these reactants R_1 is aryl, alkyl, carbalkoxy, or alkoxy, each of which has a maximum of 8 carbon atoms. Several of the R_1 residues which are particularly useful are phenyl, nitrophenyl, trifluoromethylphenyl, halophenyl, lower alkyl, carbomethoxy, carbethoxy or lower alkoxy. Since an acyl group



is eliminated during the reaction, the specific character of the R_1 group is unimportant other than being readily available, stable under the reaction conditions and sufficiently activating to make the adjacent methylene group reactive.

This process is carried out by reacting substantially equimolar quantities of the acylmethylene compound (II) and *o*-nitrosoamine (III) in a solvent in which the reactants are substantially soluble such as in a lower alkanol preferably ethanol or methanol, N,N-dimethylformamide, N,N - dimethylacetamide, or aqueous mixtures thereof. The reaction is usually run at elevated temperatures for instance at from about 65°C. to the reflux temperature of the reaction mixture for from about 1/2 to about 24 hours. The preferred conditions are in methanol or ethanol solvent or aqueous mixtures thereof at reflux usually with an excess of cyanide ions or a basic condensing agent for from about 1/2 to 16 hours. Other conditions have not been found to marked advantage except as described hereafter.

The scope of the process of this invention in preparing each of the heterocyclic systems will be readily apparent to one skilled in the art. This scope is exemplified by the following discussion in the very important 7-aminopyrimido[4,5-b]pyrazine (pteridine) series. These compounds are particularly useful as diuretic or antihypertensive compounds or as intermediates for preparing such compounds. The scope is illustrated as follows:



IV V

in which Y, R and R_1 are defined as above;

R_2 is aryl, amino, lower alkylamino, di-lower alkylamino, cyclic amino such as piperidinyl, alkyl, hydrogen, hydroxy or alkylthio, all having a maximum of 12 carbon atoms. The preferred groups are phenyl, amino or lower alkylthio.

R_3 is an amino, lower alkylamino, di-lower alkylamino, hydrogen, cyclic amino such as piperidino, alkyl, hydroxy or alkylthio, all having a maximum of 8 carbon atoms. Preferred is the amino moiety.

One skilled in the art will recognize of course that the processes of this invention are

not applicable in certain instances where the nitrosoamine starting material cannot be prepared. This is particularly true in the benzene and pyridine series. Completely representative starting materials have been mentioned which outline this choice clearly. For instance o-nitrosoaniline or 3-nitroso-2-aminopyrimidine cannot be prepared due to lack of reactivity amine parent to nitrosation or self-condensation. The amine or hydroxy substituted analogues are readily available (see Heterocyclic Compounds, *14* II 481). In the preferred pteridine series, the nitroso starting materials are easily prepared over a full range of substituents as exemplified hereafter.

The following examples will make the use of the process of this invention apparent to one skilled in the art and should not be construed as limiting the scope of this invention thereto.

EXAMPLE 1

A mixture of 8.6 g. of (0.04 mole) of 4,6-di-amino - 5 - nitroso - 2 - phenylpyrimidine, 6 g. (0.12 mole) of sodium cyanide, 19.2 g. [0.12 mole, prepared from ethyl benzoate and propionitrile as described in J. Am. Chem. Soc., *54*, 2962 (1932)] of α-benzoylpropionitrile and 250 ml. of 80% ethyl alcohol is heated under reflux for 4 1/2 hours. The mixture is concentrated to 50 ml. *in vacuo*. Cooling separated 4,7 - diamino - 6 - methyl-2 - phenylpteridine; pale yellow needles from methanol, m.p. 308—309°C.

EXAMPLE 2

A mixture of 2.15 g. of 4,6 - diamino - 5-nitroso - 2 - phenylpyrimidine, 2.6 g. of α-cyanoethyl propionate (Boone, Perkin Soc. *67*, 421), 1.0 g. of sodium cyanide, 10 ml. of water and 30 ml. of ethyl alcohol is heated at reflux for 24 hours. Concentrating and cooling gives 4,7 - diamino - 6 - methyl - 2-phenylpteridine, m.p. 308—309°C.

EXAMPLE 3

A mixture of 1.3 g. of 4,6 - diamino - 2-methylthio - 5 - nitrosopyrimidine, 1.5 g. of potassium cyanide, 3.5 g. of α-benzoylpropionitrile, 1.5 g. of sodium cyanide in 200 ml. of aqueous isopropanol is heated at reflux for 15 hours. Cooling and evaporation gives the desired 4,7 - diamino - 2 - methylthio - 6-methylpteridine, m.p. 305°C.

EXAMPLE 4

A mixture of 120 g. of ethyl benzoate and 43.2 g. of sodium methoxide is stirred at 80°C. for two hours while 86 g. of cyclohexylacetonitrile [J. Org. Chem. *25*, 877 (1960)] is added gradually. The reaction mixture is maintained at 115—120°C. for 10 hours, then diluted with an ice-water slurry in the cold. Ether is added and the aqueous layer acidified. The organic layer is taken off, washed, dried and distilled to give α-benzoylcyclohexylacetonitrile, b.p. 165—190°C./1 mm., m.p. 45—46°C.

A mixture of 1.4 g. of 4,6 - diamino - 5-nitroso - 2 - phenylpyrimidine, 3.5 g. of sodium cyanide, 23.7 g. of the nitrile, 60 ml. of water and 180 ml. of ethanol is heated at reflux for 36 hours then isolated as described to give 6 - cyclohexyl - 4,7 - diamino - 2- phenylpteridine, m.p. 338—340°C. from dilute acetic acid.

EXAMPLE 5

A mixture of 1.7 g. of α-benzoylbutyronitrile [prepared as in Dorsch, J. Am. Chem. Soc., *54*, 2960 (1932)], 1.07 g. of 4,6-diamino - 5 - nitroso - 2 - phenylpyrimidine, 0.5 g. of sodium cyanide, 10 ml. of water and 30 ml. of ethyl alcohol is heated under reflux for 8 hours. After cooling and separation, 4,7-diamino - 6 - ethyl - 2 - phenylpteridine m.p. 276—280°C., is obtained.

EXAMPLE 6

A mixture of 12.9 g. of 4,6 - diamino - 5-nitroso - 2 - phenylpyrimidine, 6 g. of sodium cyanide, 27 g. of α-benzoylphenylpropionitrile (m.p. 80—81°C.), 15 ml. of water and 225 ml. of ethanol is heated under reflux for 20 hours. The solvent is removed under diminished pressure. The residue is suspended in water and filtered to give 6 - phenyl - 4,7-diamino - 2 - phenylpteridine, m.p. 280—281°C.

EXAMPLE 7

A mixture of 2.4 g. of α - benzoyl - 4- (N-piperidino) - butyronitrile [m.p. 96—97°C., prepared from ethyl benzoate and 4 - (N-piperidino) - butyronitrile], 1.2 g. of 4,6-diamino - 5 - nitroso - 2 - phenylpyrimidine, 0.8 g. of potassium cyanide and 50 ml. of aqueous methanol is heated at reflux for 8 hours. Working up as described gives 2-phenyl - 4,7 - diamino - 6 - β - piperidinoethylpteridine.

EXAMPLE 8

A mixture of 2 g. of 3 - nitroso - 2,6-diaminopyridine, 4.5 g. of α-benzoylpropionitrile, 1.5 g. of sodium cyanide in aqueous ethanol is heated at reflux for 18 hours then worked up as described to give 3,6-diamino-2-methylpyridopyrazine.

EXAMPLE 9

A mixture of 2.4 g. of α-benzoyl-bromoacetamide, 2 ml. of pyridine and 20 ml. of absolute ethanol is heated briefly then added to a mixture of 1.2 g. of 4,6 - diamino - 5-nitroso - 2 - phenylpyrimidine, 0.5 g. of sodium cyanide, 10 ml. of water and 50 ml. of ethanol. Warming on a hot plate causes instantaneous reaction giving yellow crystals of 4,7 - diamino - 2 - phenyl - 6 - pteridinecarboxamide.

EXAMPLE 10

A mixture of 1 g. of propiophenone-o-pyridinium bromide (prepared from the halide

by reaction with an excess of pyridine in alcohol), 0.3 g. of 4,6 - diamino - 5 - nitroso-2 - phenylpyrimidine, 0.19 g. of sodium cyanide and 20 ml. of aqueous methanol is heated at reflux for 4 hours. Cooling and concentration gives the desired 4,7-diamino-2-phenyl-6-methylpteridine.

EXAMPLE 11

A mixture of 2.5 g. of ethyl α-bromophenylacetate, 2 ml. of lutidine and 50 ml. of methanol is warmed, then added to a warmed mixture of 1.6 g. of 2,4,6-triamino-5-nitrosopyrimidine, 0.7 g. of potassium cyanide and 50 ml. of aqueous isopropanol. The mixture is then heated at reflux for 48 hours. Evaporation, cooling and fractional crystallization give 2,4,7-triamino-6-phenylpteridine.

WHAT WE CLAIM IS:—

1. A process for preparing heterocyclic compounds of the structure:

in which R is an unsubstituted or substituted alkyl or aryl group having a maximum of 12 carbon atoms, alkoxy having a maximum of 8 carbon atoms, phenoxy or carbamyl, and X together with the two carbon atoms to which it is attached represents an optionally substituted phenyl, naphthyl, pyrimido, pyrazolo or pyrido ring, comprising reacting with an α-nitrosoamine of the structure:

an acylmethylene compound of the structure

in which R_1 is aryl, alkyl, carboalkoxy or alkoxy, each having a maximum of 8 carbon atoms, and

(1) Y is cyano when R is as defined above, in the presence of a basic condensing agent;

(2) Y is pyridinium or substituted pyridinium when R is as defined above, in the presence of cyanide irons, and

(3) Y is hydrogen when R is aryl or carbamyl, in the presence of cyanide ions, said process being further characterized in the concurrent elimination of an acyl radical,

during the reaction.

2. The process of claim 1 characterized in that X represents an optionally substituted pyrimido ring.

3. The process of claim 1 characterized in that a 4,6-diamino-5-nitropyrimidine and an acylmethylene compound of the structure

in which R_1 is aryl, alkyl, carboalkoxy or alkoxy, Y is a pyridinium or substituted pyridinium and R is as defined, are reacted in the presence of an excess of cyanide ions.

4. The process of claim 1 characterized in that a 4,6-diamino-5-nitrosopyrimidine and an acylmethylene compound of the structure:

in which R_1 is aryl, alkyl, carboalkoxy or alkoxy and R is as defined above are reacted in the presence of an alkaline condensing agent.

5. The process of claim 1 characterized in that a 4,6-diamino-5-nitropyrimidine and an acylmethylene compound of the structure:

in which R_1 is aryl, alkyl, carboalkoxy or alkoxy and R is aryl or carbamyl are reacted in the presence of cyanide ions.

6. A process for preparing a heterocyclic compound of the structure defined in Claim 1, substantially as described in any one of Examples 1 to 8 of the foregoing Examples.

7. A process for preparing a heterocyclic compound of the structure defined in Claim 1, substantially as described in any one of Examples 9 to 11 of the foregoing Examples.

8. A heterocyclic compound whenever prepared by the process claimed in any preceding Claim.

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